REMARKS

After entry of the foregoing amendments, Claims 22-29, 32-33 and 35-36 have been amended. By the foregoing amendments, Claims 30-31 are cancelled without prejudice. Therefore, Claims 22-29 and 32-41 remain present for examination. The amended claims are supported by the specification and the claims as originally filed. No new matter has been added. The specific changes to the amended claims are shown above with the insertions being underlined and the ~~deletions shown stricken through.~~

Applicants respond below to the formal matters and to the specific rejections and objections raised by the Examiner in the Office Action of March 20, 2003.

Discussion of Formal Matters

Priority:

The Office Action granted priority to the filing date of PCT/US00/05601, filed on March 1, 2000. Applicants acknowledge the date of March 1, 2000 for examination of the instant claims. Applicants make no admission as to the propriety of that date for priority and reserve the right to later address the same.

Title Objection:

According to the Office Action, the title of the invention was not descriptive. The title has been amended as set forth above to be more descriptive of the invention set forth in the elected claims. Therefore, Applicants request withdrawal of the objection to the title.

Claim Objections:

Claims 22-33 and 35 were objected to for identifying a sequence by reference to a figure with the SEQ ID NO in parenthesis. As set forth above, Claims 30-31 have been cancelled and Claims 22-29, 32-33 and 35 have been amended to refer to the nucleic acid sequence or the amino acid sequence by referring to a SEQ ID NO. Thus, Applicants respectfully request withdrawal of the objections to pending Claims 22-29, 32-33 and 35.

Discussion of Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 22-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action alleges that Claims 22-27, 30, 31 and 35 are not clear because they recite "the extracellular domain." Claim 36 also was rejected as being indefinite for allegedly omitting essential elements related to the hybridization conditions.

As set forth above, Claims 30-31 have been cancelled and Claims 22-27 and 35 have been amended to remove reference to "the extracellular domain." In view of the amendments to Claims 22-27, 30-31 and 35, the claims are clear and definite. Therefore, withdrawal of the § 112, second paragraph, rejections is respectfully requested.

Claim 36 as amended is clear and definite because specific stringency conditions are recited in the claim. Support for the recited stringency conditions is found in the specification at page 80, lines 10-14. The stringency conditions are easily understood and practiced by any skilled artisan. Thus, Claim 36 as amended is clear and definite.

Therefore, withdrawal of the § 112, second paragraph, rejections is respectfully requested.

Discussion of Rejections under 35 U.S.C. § 112, First Paragraph

Enablement

Claims 22-27, 30-31, and 35-41 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Office Action, the specification is enabling for claims limited in scope to a nucleic acid having the sequence of SEQ ID NO:1, and a nucleic acid encoding a polypeptide having the sequence of SEQ ID NO:2. However, according to the Office Action, the specification does not reasonably provide enablement for claims to various percentage variants and fragments of the sequence of SEQ ID NO:1, or for percentage variants and fragments of the nucleic acid sequence encoding a polypeptide having the sequence of SEQ ID NO:2. Further, the Office Action alleges that the specification does not provide enablement for the hybridization variants.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing

more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Amended Claims 22-27, as well as Claims 35-41 are enabled. Claim 27 has been amended to remove reference to "the extracellular domain." As stated in the Office Action, claims to a nucleic acid having the sequence of SEQ ID NO:1, and a nucleic acid encoding a polypeptide having the sequence of SEQ ID NO:2, are enabled. Thus, amended Claim 27 is enabled.

Claims 22-26 and 35-41 also are enabled. As set forth above, Claims 22-26 have been amended to remove reference to "the extracellular domain." Also, Claims 22-26 and 35 have been amended to include a functional limitation associated with the percentage variants and hybridization variants, specifically, that the isolated nucleic acid encodes a polypeptide that has the ability to induce chondrocyte redifferentiation.

The claims as amended are enabled because, given the teaching of the specification, one of ordinary skill in the art can easily make and use the isolated nucleic acids, which have the ability to induce chondrocyte redifferentiation, without undue experimentation. For example, the specification at pages 109-122 provides detailed teaching on how to make polypeptide fragments and variants, and the corresponding nucleic acid fragments and variants, and also provides uses for the nucleic acids of various lengths. Those teachings include, for example, how to make variations in the full-length native sequences, how to make fragments, how to make substitutions and how to make modifications.

Furthermore, Example 36 at page 166 of the specification provides working examples and an assay protocol for determining if a polypeptide induces redifferentiation of chondrocytes.

Regarding Claim 35, according the Office Action, the claim reads on any or all nucleotides hybridizing to the sequence of SEQ ID NO:1 or to those encoding the polypeptide having the sequence of SEQ ID NO:2. The specification at pages 79-80 describe hybridization conditions and methodology. Furthermore, Claim 35 has been amended to recite the functional limitation that the isolated nucleic acids encode polypeptides having the ability to induce

chondorocyte redifferentiation, as taught in Example 36 on page 166. Therefore, amended Claim 35 is enabled because one of ordinary skill in the art can easily make and use the claimed hybridization variants with the recited function.

Further, with regard to Claim 37, the Office Action states the claim is not enabled because nucleotide fragment of the hybridization variant of Claim 35 may comprise 10 nucleotides which have no sequence homology to the sequence of SEQ ID NO:1 or to those encoding the polypeptide having the sequence of SEQ ID NO:2. Respectfully, Claim 37 is enabled because one of ordinary skill in the art can easily make and use the recited nucleic acid sequences. Claim 37 depends from amended Claim 35. One of ordinary skill in the art, having possession of the isolated nucleic acid sequence of Claim 35, can easily make an isolated nucleic acid of at least 10 nucleotides therefrom. Also, the specification discusses various types of and uses for nucleic acid fragments. For example, pages 119-120 provide, for example, the use of fragments as hybridization probes, as antisense and sense oligonucleotides, as PCR primers and probes, as mapping probes, and the like. Therefore, Claim 37 reciting the isolated nucleic acid of Claim 35 which is at least 10 nucleotides in length is enabled because Claim 35 is enabled and the specification explains how to make and use the various fragments.

Thus, the specification provides ample guidance and direction for making and using the claimed isolated nucleic acids with little or no experimentation. One of ordinary skill in the art can easily follow the teachings of the specification to make nucleic acid percentage variants and hybridization variants as specified in the claims. The skilled artisan also can easily determine using the assay of Example 36 that the encoded polypeptide variants have the claimed functionality. Therefore, enablement is commensurate in scope with the amended claims. For these reasons, reconsideration and withdrawal of the enablement rejection in view of the amendments to the claims is respectfully requested.

Written Description

Claims 22-27, 30-31 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors possessed the claimed invention at the time of filing the application. According to the Office Action, the claims are

drawn to a genus of nucleic acids that is defined only by sequence identity; the claims do not require, *inter alia*, that the nucleic acids encode polypeptides that possess any particular biological acitvity.

To satisfy the written description requirement, a patent application must describe the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991). All disclosed distinguishing identifying characteristics are to be considered, including the level of skill and knowledge in the art, partial structures, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, method of making, and any combinations thereof. *See* M.P.E.P. § 2163.

Amended Claim 27 is fully described because the specification provides the sequence for the isolated nucleic acid as recited in the claims. Also, Claim 27 has been amended to remove reference to "the extracellular domain." Certainly, the specification describes both an isolated nucleic acid comprising a nucleic acid sequence encoding the polypeptide having the sequence of SEQ ID NO:2 and a nucleic acid encoding the polypeptide having the sequence of SEQ ID NO:2 lacking its associated signal peptide. Similarly, the specification certainly describes an isolated nucleic acid comprising a nucleic acid having the sequence of SEQ ID NO:1, the full-length coding sequence of the nucleic acid having the sequence of SEQ ID NO:1, and the full-length coding sequence of the cDNA deposited under ATCC accession number 203581. Therefore, Claim 27 is fully described.

Also, amended Claims 22-26, and Claims 35-37 are described in sufficient detail to show possession of the claimed invention by the inventors at the time of filing the application. Claims 22-26 require sequence identity to one of the recited nucleic acid sequences. Claim 35 requires that the isolated nucleic acid hybridize with one of the recited nucleic acid sequences. In addition, as discussed above, Claims 22-26 and 35 have been amended to include the functional limitation for biological activity that the isolated nucleic acid encodes a polypeptide having the ability to induce chondrocyte redifferentiation. In view the requirement for sequence identity or hybridization, and in view of the amendment adding the functional limitation, the independent claims and the claims depending therefrom, are fully described because the genus of isolated

nucleic acids is described by sufficient identifying characteristics to show possession. Reconsideration and withdrawal of the written description rejection is therefore respectfully requested.

Discussion of Rejections under 35 U.S.C. § 102

Claims 22-27, 30-31 and 35-41 were rejected under 35 U.S.C. § 102(b) as being anticipated by Dumas et al., WO 99/06551-A2 (referred to hereafter as "Dumas"). Also, Claims 22-25 and 35-42 were rejected under § 102(a) as being anticipated by Strachan et al., WO 99/55865-A1. Finally, Claims 22-25 and 35-41 were rejected under 35 U.S.C. § 102(e) as being anticipated by Strachan, U.S. Patent No. 6,150,502.

Dumas, Strachan et al. and Strachan do not anticipate Claims 22-27 or Claims 35-41. To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ... There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Dumas § 102(b) Rejection

According to the Office Action, Dumas discloses a nucleic acid sequence identical with nucleotides 1-449 of SEQ ID NO:1 and which encode a polypeptide that has amino acids 1-124 of SEQ ID NO:2. Therefore, the Office Action asserts that Dumas anticipates the claims "as being a nucleic acid having at least 99% sequence identity to a nucleic acid sequence encoding the extracellular domain of the polypeptide having the sequence of SEQ ID NO:2 or as being a nucleic acid hybridizing to a nucleic acid encoding the extracellular domain of the polypeptide having the sequence of SEQ ID NO:2." The Office Action also states that Dumas anticipates Claims 38-41 because Dumas discloses an expression vector, control sequences, and a host cell comprising the vector.

Dumas does not anticipate the Claims 22-27 and 35 as amended. The Office Action asserted that Dumas anticipated the element of the claims that related to "the extracellular domain." However, as mentioned above, Claims 22-27 and 35 have been amended to remove reference to "the extracellular domain."

Dumas also does not disclose isolated nucleic acids as otherwise recited in the amended claims. Dumas does not disclose, for example, an isolated nucleic acid having 80% nucleic acid identity to a nucleic acid sequence encoding the polypeptide having the sequence of SEQ ID NO:2 or encoding the polypeptide having the sequence of SEQ ID NO:2 lacking its associated signal peptide. The isolated nucleic acid sequence disclosed by Dumas encodes a polypeptide that is only identical to 50.4% of the polypeptide having the sequence of SEQ ID NO:2. Identity of 50.4% is far less than the 80% sequence identity recited in Claim 22, for example. Therefore, Dumas disclosed a different nucleic acid sequence.

Dumas also did not disclose an isolated nucleic acid, for example, having at least 80% nucleic acid sequence identity to the nucleic acid having the sequence of SEQ ID NO:1, or the full-length coding sequence of SEQ ID NO:1. Dumas does not anticipate because it disclosed a nucleic acid sequence that is only identical to 27.6% of SEQ ID NO:1, and only 63.7% identical to the coding region of SEQ ID NO:1.

Therefore, Dumas does not anticipate Claims 22-27.

Furthermore, Claims 22-26 as amended require that the isolated nucleic acid sequence encode a polypeptide that has the ability to induce chondrocyte redifferentiation. Dumas does not teach a polynucleotide encoding a polypeptide having the ability to induce chondrocyte redifferentiation.

Claim 35 is not anticipated because Dumas does teach an isolated nucleic acid that hybridizes to the recited nucleic acid sequences and Dumas does not disclose a nucleic acid which encodes a polypeptide having the ability to induce chondrocyte redifferentiation. Dumas discloses a different encoded polypeptide, that is one having only 50.4% identity with the polypeptide having the sequence of SEQ ID NO:2, and Dumas does not disclose that the polypeptide has the ability to induce chondrocyte redifferentiation.

Therefore Dumas does not anticipate because it does not teach each and every limitation of the claims.

Strachan § 102(a) Rejection

According to the Office Action, Strachan et al. discloses a polynucleotide sequence with 96% sequence similarity to a nucleic acid sequence encoding SEQ ID NO:2. Therefore, the Office Action asserts that Strachan et al. anticipates Claims 22-25 and 35-41 as being a nucleic acid having at least 95% sequence identity to a nucleic acid sequence encoding the polypeptide having the sequence of SEQ ID NO:2, or a sequence hybridizing to the nucleic acid sequence encoding the polypeptide having the sequence of SEQ ID NO:2.

Claims 22-25 and 35 as amended require that the isolated nucleic acid encode a polypeptide that has the ability to induce chondrocyte redifferentiation. Strachan et al. does not teach an encoded polypeptide having the ability to induce chondrocyte redifferentiation. the polynucleotide disclosed by Strachan et al. is only 54.3% identical to the nucleic acid sequence of SEQ ID NO:1 and 89.47% homologous to the coding region of the nucleic acid sequence of SEQ ID NO:1. Furthermore, the encoded polypeptide disclosed by Strachan has only 39.8% identity to the polypeptide encoded by SEQ ID NO:1, and is therefore, significantly different. Strachan does not teach that the encoded peptide has the ability to induce chondrocyte redifferentiation. Therefore Strachan et al. does not anticipate because it does not teach each and every limitation of the claims.

The Office Action stated that Strachan, U.S. Patent No. 6,150,502, anticipates Claims 22 25 and 35-411 under § 102(e) for the same reason as stated above with regard to Strachan et al. Thus, for the same reasons set forth above, Strachan also does not anticipate the claims.

Applicants, therefore, request that the Examiner reconsider and withdraw the rejections based on 35 U.S.C. § 102.

CONCLUSION

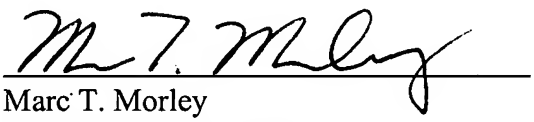
Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the cosmetics of the claims. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 6/20/03

By: 

Marc T. Morley
Registration No. 52,051
Attorney of Record
Customer No. 30,313
(619) 235-8550

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